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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/679,776 | 10/05/2000 | Richard D. Granstein | 2650/1F966-US1 | 8709 |

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| EXAMINER |
|---|
| LI, QIAN J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 8 |

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/679,776 | Applicant(s) GRANSTEIN, RICHARD D. |
|---|---|---|
| | Examiner Janice Li | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment filed on September 29, 2001 has been entered as Paper #7. Claims 16 and 24 have been amended, claim 31 is newly added. Claims 1-31 are pending in the application and under current examination.

The Declaration filed on September 20, 2001 under 37 CFR 1.131 is sufficient to overcome the *Nair et al*, and *Zhang et al* references.

The Declaration under 37 CFR 1.132 filed on September 20, 2001 is sufficient to overcome certain aspect of rejection of claims 1-30 under 35 U.S.C. 112, first paragraph which is based upon i.v. administration of total tumor cellular RNA.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph stands and applies to the newly added claim 31, because the specification, while being enabling for reducing tumor cell load in experimental fibrosarcoma in mice, does not reasonably provide enablement for reducing tumor cell load for all tumors, or treating any tumor in human, and it does not reasonably provide enablement for protecting a subject from any and all pathogens such as microbial pathogens, or for inducing tolerance to any and all antigens by any routes of administration. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The applicant argues in Paper #7 that the materials and methods for obtaining total cellular RNA, or antigen-specific RNA, for delivering the RNA into cells, or for preparing RNA vaccines are considered to be routine in this field and fully addressed in the specification, thus, the specification provides full enabling support for claims 1-30; that references cited, such as *Eck et al,* are dated and merely provide a general survey of the field, and do not specifically address the claimed invention. Thus, the examiner has not provided a specific scientific basis for attacking enablement of the claimed invention.

In response, the argument has been carefully considered but found not persuasive, because the Office never questioned the methods of prosecuting the invention, but the unpredictable outcome of the invention as it broadly claimed. The enablement in question is whether the therapeutic anti-tumor effects would be achieved in human, whether a protective effect would be achieved to any types of pathogens and antigens, such as microorganisms, allergens, allograft antigens, and autoantigens. The aspects of insufficiency for enablement are discussed in detail advanced in Paper #5, pages 2-7, which are supported not only by the general survey of the field such as *Eck et al*, but also by other up-to-date specific references addressing specific scientific issues regarding RNA vaccine, and vaccination in general to different antigens and diseases. For example, *Mitchell et al* (Curr Opin Mol Ther 2000 Apr;2:176-181), who teach underdeveloped state of RNA vaccination that is yet far from protecting a human

subject from cancer, the factors for such limitation, and particularly why intravenous route of delivery is in question for RNA vaccination; *McCluskie et al* (Mol Med 1999 May;5:287-300), who teach how routes of administration would influence the strength and nature of an immune response, and how promising results in animal models have not realized in human trials; and *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5), who teach that host cell resistance to foreign gene is another barrier for successful gene therapy. Moreover, it is well known in the art that immune system uses different mechanisms to deal with different offenders, such as tumors, microbial, transplant antigens, and autoantigens, thus, the solution may not be the same as discussed particularly in the 3rd paragraph of page 5, Paper #5. For example, if HIV pathogen mRNA were to give to HIV tumor patients, what would be the outcome? If the RNA of an autoantigen or graft cell antigens were to give to patients having autoimmune disease or about to accept a foreign tissue, what would be the outcome of taking such cellular RNA? The fact is that mechanism for autoimmunity and graft rejection is so complicated and yet unclear in the art, the outcome would be highly unpredictable for a skilled artisan to practice the claimed invention as it broadly claimed. Considering another aspect of tumor immunity, a mice fibrosacoma model does not appear to be a valid model for human fibrosacoma, because the mechanism of fibrosacoma in human is distinct from injection of tumor cells, thus it is highly unpredictable if the RNA is to apply to human fibrosacoma patients. As such, the Office has provided reasonable and specific scientific basis for questioning the enabling support of the broad claims.

Furthermore, The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of gene therapy and nucleic acid vaccination. "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC". (In re *Marzocchi* 169 USPQ 367 (CCPA)). When instant claims read on a method for the protection and treatment of any immunological, infectious and malignant diseases, a doubt is reasonable since RNA or genetic vaccination has yet to become standard practice in the art for these diseases as of today.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement for the broad scope.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of claims 1-3, 5, 7, 8, 9, 11, 24, and 28-30 under 35 U.S.C. 102(e) as being anticipated by *Nair et al* (IDS) is withdrawn in view of the Declaration under Rule 131.

The rejection of claims 24 and 29 under 35 U.S.C. 102(a) as being anticipated by *Zhang et al* (Hum Gene Ther 1999 May 1;10:1151-61) is withdrawn in view of the Declaration under Rule 131.

Claims 24 and 30 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Qiu et al* (Gene Ther 1996;3:262-68) for the reason of record and set forth following.

Applicants argue that *Qui et al* does not deliver a tumor antigen RNA, but RNA of reporter proteins. In response, the claim recitation does not limit the antigen to a tumor antigen, but broadly " an antigen", because an antibody immune response is triggered, the reporter proteins are considered as an antigen relative to the antibody. Applicants further argue that *Qui et al* does not teach a pharmaceutical carrier suitable for human. However, the art-known carrier composition used for gene gun delivery does not appear different in animal models and in human. In the working example, the pharmaceutical carrier for the RNA is normal saline, which could be used in both human and animal. Thus, the argument is not persuasive. *Qiu et al* still anticipate the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-3, 5, 7, 8, 9, 11, 12, 24, 28, and 30 under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al* (Hum Gene Ther 1999 May 1;10:1151-61), taken with *Nair et al* (IDS) is withdrawn in view of the Declaration under Rule 131.

The rejection of claims 1-5, 7, 8, 9, 11, 24, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over *Qiu et al* (Gene Ther 1996;3:262-68), taken with *Nair et al* (IDS) is withdrawn in view of the Declaration under Rule 131.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 15, 2001

JAMES KETTER
PRIMARY EXAMINER